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EXAMINER	
NOLAN, S	
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This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-74 are pending in the application.
   Of the above, claims 1-38 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 39-74 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to teach how to made and use the invention .

The methods involving co-tranformation of a host with a 2 vectors, one comprising sequences coding for a heterologous protein and one comprising GS sequences, are not taught in the specifications. There is no suggestion in the disclosure of co-amplification of non-contiguous DNA fragments as would be required in this embodiment. The embodiment would require undue experimentation to duplicate given the absence of guidance and the unpredictability of the technology employed.

Claims 62,64-69, and 72-74 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 51,53,54,55,62-69, and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to materials used in the examples or those closely related to such materials. See MPEP 706.03(n) and 706.03(z).

Claims 51 and 53 imply several functions which are usually highly species specific. For instance, it is unlikely that an expression vector which operates in CHO cells would operate the same way in abacterial cell, yeast cell or possibly other mammalian cells. It is unlikely that the vector which is an expression vector in CHO cells would transform into or replicate in cells of distantly-related species.

Similarly, claims 54 and 55 recite a regulatable promoter and two examples of such without notation of the species from which the promoters were derived nor the species in which the promoters are expected to function. For the same reasons as noted above the disclosure is not considered enabling for all possible interpretations of the claim language.

Claims 62-69 and 72-74 present similar problem as is seen with claims 51,53,54, and 55 In addition, claims 62-69 and 72-74 require that the host cell contains the machinery necessary to effect amplification of those particular sequences. Such machinery would be expected to be host specific.

Claims 44,48,49, and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is incomplete.

A proper method claim is expected to recite all essential steps in a positive manner. The term "a hybridisation probe" does not adequately describe the method of use.

Claim 44 is confusing; it is not clear what is the antecedent basis of "part thereof" nor what is the antecedent basis of different species (i.e different from what?).

Claims 39 and 49 are duplicate in scope; product defined by use does not further limit the claim. The term "such as" is improper claim language as it is indefinite in scope. Medical or diagnositc methods is unduly alternative as medical and diagnositc methods are often quite different from one another. If claim 49 is intended to be a method claim, please recite all essential steps of the method in a positive manner.

Claim 69 is unclear; it is not entirely clear what is meant by "switched on" and "down regulated". If this is meant to imply by manipulation of a regulatable promoter or by metabolic control please state as such.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 39-43,45-50, and 61 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders in view of Pennica et al.

Sanders et al teach the amplification and cloning of the Chinese hamster glutamine synthetase gene.

Pennica et al teach cloining of human tPA using a variety of recombinant DNA techniques.

Claim 39-43,45-47, and 49-50 recite a variety of recombinant DNA molecules comprising the sequences which code for hamster glutamine synthetase. Claim 48 recites the use of the recombinant DNA of claim 39 as a hybridization probe. claim 61 recites a host cell transformed with a vector according to claim 50.

The difference between the clone of Sanders et al and that of claims 39-43 and 45-46 is that the sequences of the instant invention code for the entire amino acid sequence rather than only part of it. Pennica et al teach a variety of techniques by which one can obtain full-length coding sequences when an abundant mRNA is present. The genomic DNA clone of claim 47 is similarly obtainable by standard techniques such as those used by Pennica. Claims 48 and 49 teach the use of a recombinant DNA as a hybridization probe (claim 48) and specifically as a hybridization probe to detect increased levels of GS mRNA (claim 49?). Sanders et al also teach use of a recombinant DNA as a hybridazation probe such as in differential colony hybridization and DNA spot hybridizations. These and other similar techniques are well known in the art.

The recombinant DNA vector of claim 50 could be any of the intermediates in the cloning procedure such as the lambda clones, etc. The host cell of claim 61 which has been transformed with a vector according to claim 50 could similarly be any intermediate host such as the bacteria in which the clones are grown.

It is within the ordinary level of skill in the art to perform such procedures as reverse transcription, colony hybridization; DNA sequencing; subcloning; and transformation of a variety of hosts.

It is a common problem of reverse transcription procedures to obtain a less than full length cDNA. Once one has a partial DNA it is obvious to use that DNA to obtain a full length cDNA , genomic DNA, etc. so that the gene may be studied or used in the desired manner.

Claim 44 is rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al in view of Young and Ringold.

Sanders et al teach cloning the hamster GS gene from a cell line which has amplified GS DNA and has abundant GS mRNA.

Young and Ringold teach overproduction of GS mRNA in mouse cells which are thought to have amplified the GS gene.

Claim 44 recites a GS-encoding DNA sequence from a mammal other than Chinese hamster which will hybridze to the clones of the instant invention.

Young and Ringold note that the mRNA prepared from their overproducing cells will be used to probe genomic and cDNA libraries to obtain the mouse GS gene. Given the close evolutionary relationship between hamsters and mice, it is likely that these two DNAs will cross hybridize. Absent evidence to the contrary it appears that the GS DNAs of these two species would hybrize under high stringency conditions.

Claims 51-53 and 56-60 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al in view of Pennica et al.

Sanders et al teach the cloning of the GS gene from Chinese hamsters.

Pennica et al teach the cloning of human tPA.

Claims 51-53 teach the cloning of the GS gene in a variety of vectors some of which also comprise the gene for tPA.

Applicants admit that the cloning vechicles they use are prior art (p.22-23). Cloning gene into a variety of known vectors is within the ordinary level of skill in the art. A given vector may be chosen for its known success in a particular host or for its convenient restriction sites. Absent unexpected results, cloning a known gene in a known vector is an obvious step and not considered patentable.

Claims 54 and 55 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al in view of Pennica et al as applied to claims 51-53 and 56-60 above, and further in view of Finkelstein.

See above for the teachings of Sanders et al and Pennica et al.

Finkelstein teaches a heat shock promoter for use in recombinant vectors.

Claims 54 and 55 teach the vector of claim 51 with a regulatable promoter such as a heat shock promoter.

The difference between the prior art and the claims is that the claims have used the promoter of Finkelstein in the system discussed above. It is within the ordinary level of skill in the art to substitute an element such as a promoter for another similar element. It is very frequently advantageous in recombinant DNA system to use regulatable promoters as overproduction of the recombinant protein(s) may harm or even kill the host cells; regulatable promoters allow the investigator to grow the transformed hosts under "non-induced" type conditions without harm to the cells and then turn on the regulator when the viability of the host cells is dispensable. Absent unexpected results, substitution of one known unit for its functional equivalent is not considered patentable over prior art.

Claims 70 and 71 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al .

Sanders et al teach the amplification of GS sequences in a GS+ cell by selecting for increased resistance to a known inhibitor of GS.

Claims 70 and 71 recite use of a GS expression vector as a dominant selectable marker in GS+ cells and as a selectable marker in GS- cells.

Applicants admit that cell lines are known which are GS- (p.8). By the work of Sanders et al it is clear that GS+ cells can increase resistance of GS inhibitors even in the absence of exogenous GS genes. Thus it is clear that multiple copies of the GS gene constitute a "dominant marker" no matter what their source, and that GS- cell can of course be complemented by a GS+ gene on functional expression vector. The latter system is a very common way by which genes are cloned. Absent unexpected results' the vectors and cells are functioning in predictable ways, and are therefore considered unpatentable over the prior art.

Claim 63 is rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al in view of Ringold.

Sanders et al teach the amplification and cloning of GS sequences in Chinese hamsters.

Ringold teaches a method of amplification of a second gene which comprises transforming a host with a DNA vector comprising an amplifiable first gene and a second gene, growing the transformed host under conditions which select for enhanced expression of the first gene, and obtaining cells in which both genes have been amplified.

The claims have used the GS clone of Sanders et al to develop expression vectors with GS and a heterogous protein.

The difference between the prior art and the claim is that the instant invention uses GS as the amplifiable-gene rather than the dihydrofolate reductase of Ringold, The "amplifiable" character of GS was previously established by Sanders et al. It is within the ordinary level of skill in the art to exchange one selectable marker for another in plasmid constructions. The GS gene is also previously known to be selectable as a dominant marker (by Sanders et al), thus the choice of the GS gene in lieu of the DHFR gene may be to use a wider variety of host cells. It appears that the GS gene functions in the expected manner.

It is therefor deemed to involve the exchange of functional equivalents to use the GS gene rather than the DHFR gene as the selectable and amplifiable marker an is therefore not patentable over the prior art.

Claims 62,64,65,69 and 72-74 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al in view of Ringold as applied to claim 63 above, and further in view of Axel et al and Pennica et al.

The method of co-amplifiation of GS sequences is as noted above. The amplification of GS sequence was seen in response to increasing levels of the GS inhibitor methionine sulphoximine in the system of Sanders et al. The Ringold system uses the DHFR inhibitor methotrexate to achieve amplifiation of the DHFR and other sequences.

Pennica et al teach the cloning of the tPA gene.

Axel et al teaches a process for inserting multiple copies of the gene for a desired protein by co-transforming the gene for the desired protein and an "amplifiable" gene for a dominant selectable marker, and then selecting for the amplification of the selectable marker by exposing the cells to increasing amounts of an inhibitor.

The difference between the claims and the prior art is that the applicants have used their GS gene is the system of co-transformation of Axel et al. The "desired" gene in this case is tPA. The host cells of Ringold are CHO cells as are those of one embodiement of the instant invention invention. The Axel et al system uses mouse cells. The choice of recipient cells is deemed to the a matter of convenience; any suitable host cell is acceptable as long as the cells are able to express and complify the appropriate genes. Claim 69 recites using a regulatable operator of the GS gene; again this requires that the host cell recognize such sequences.

In the absence of unexpected results, the substitution of one selectable gene for another, or one heterogous gene for another, or one type of regulator sequence for another is not considered patentable over the prior art. All of the composite elements are previously known and appear to function in the expected manner.

Claim 66 is rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al Ringold, Axel et al and Pennica et al as applied to claims 62-65, and 72-74 above, and further in view of Donn et al.

The instant invention is taught by the references as noted above.

Donn et al teach the amplification of the alfalfa GS gene by treatment of alfalfa cells with the GS inhibitor phosphinothricin.

Claim 66 recites the method of claim 65 wherein the GS inhibitor is phosphinothricin or methionine sulfhpoximine.

It is within the ordinary level of skill in the art to use a compound known to inhibit GS and cause amplification of GS genes for its known properties. The choice of specific GS inhibitors is considered a matter of investigators choice. Use of a known compound for its known properties is not considered patentable over prior art.

Claims 67 and 68 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al, Ringold, Axel et al, and Pennica et al as applied to claims 62-65, 69, and 72-74 above, and further in view of Young and Ringold.

The instant invention is taught by the references as noted above.

Young and Ringold discuss the regulation of the mammalian GS enzyme.

The regulation of enzyme levels or activities by adding end products or inhbitor analogs is within the ordinary level of skill in the art and is not deemed patentable over the prior art.

Any inquiry concerning this communication should be directed to Sherry Nolan at telephone number 703-557-0938.

Nolan/kfo

5/17/89 5/22/89 SKN 5-23-89

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ART UNIT 185